REMARKS

1. Formal Matters

a. Status of the Claims

Claims 23-38 are pending in the instant application. Claims 24, 26-30, 32 and 34-38 are hereby canceled without prejudice to pursuing the canceled subject matter in a continuing application. Claims 23 and 25 are amended. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the instant application. Upon entry of these amendments, claims 23, 25, 31, and 33 are pending and under active consideration.

b. Amendments to the Claims

Support for the amended claims can be found in the application as originally filed as described in Table A.

Table A

Claim	Support
23	Table 7, lines 312,839-313,772; paragraph 0044; paragraph 0047; paragraphs 0143-0147
25	Table 7, lines 312,839-313,772; paragraph 0044; paragraph 0047; paragraphs 0143-0147

c. Interview Summary

The undersigned would like to thank Examiners Wollenberger and Angel for the courtesy of the personal interview conducted on November 8, 2007, at which the utility rejection was discussed.

2. Patentability Remarks

a. 35 U.S.C. § 112, Second Paragraph

On pages 2 and 3 of the Office Action, the Examiner rejects claims 23-38 and 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner asserts that the limitation "RNA equivalent" of claim 23 is unclear. Amended claims 23 and 25 no longer recite this limitation. Claims 24, 26-30, 32, and 34-38 are canceled, thereby rendering moot the rejection of these claims. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 23-38 under 35 U.S.C. § 112, second paragraph.

b. 35 U.S.C. § 101

On pages 3-10 of the Office Action, the Examiner maintains the rejection of claims 23-38 under 35 U.S.C. § 101, for allegedly lacking utility. In order to satisfy the utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as established in the art, and the utility must be credible. *See In re Fisher* 421 F.3d 1365, 1371 (2006) and *Revised Interim Utility Guideline Training Materials* ("Guidelines").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See In re Fisher* 421 F.3d at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a specific utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and *Guidelines*.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs were from a cDNA library of pooled leaf tissue isolated from a maize plant. The Fisher application did not disclose the location of the ESTs in the genome or the function of the underlying genes. Fisher asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) provide a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Id.* at 1367-1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids maybe used to target and modulate expression of **specific** gene transcripts. Table 7, lines 312,839-313,772 and Table 7A, lines 15144-15148 of the application disclose that the claimed microRNA-related sequences specifically target mRNA transcripts of the MGAT5 gene. Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target gene MGAT5**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating the MGAT5 gene.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. *See In re Fisher* at 1371 and

Guidelines. Applicant respectfully submits that the application provides a substantial utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and *Guidelines*.

In Fisher, it was admitted that the underlying genes for the ESTs had no known function. Fisher argued that this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, Fisher failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Id.* at 1373, quoting *Brenner v. Manson*, 383 U.S. 519 (1966).

In further sharp contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of MGAT5. *See* Table 7A, lines 15144-15148. At the time of filing, it was known in the art that MGAT5 is a Golgi enzyme β1,6 N-acetylglucosaminyltransferase V. *See* Granovsky M, *et al.* (*Nat Med* 2000;6(3):306-12) ("Granovsky"). MGAT5 was known to be required for the biosynthesis of β1,6GlcNAc-branched N-linked glycans attached to cell surface and secreted glycoproteins, and that MGAT glycan products were commonly increased in malignancies. *Id.* Furthermore, Mgat5 -/- mice were known to be less susceptible to mammary tumor growth and metastases induced by the polyomavirus middle T oncogene. *Id.*

It was additionally known that Mgat5-/- tumor cells were less responsive than wild-type cells to signaling via EGF, IGF, PDGF, bFGF, fetal calf serum, and TGFβ. *See* Partridge EA, *et al.* (*Science* 2004;306:120-4). Infecting the cells with a Mgat5-expressing retroviral vector could restore TGFβ signaling in mutant Mgat5 cells. *Id.* Consistent with the decreased sensitivity of cells to signaling when they are mutant for Mgat5 and the reduction in tumor cell proliferation in Mgat5-/- mice, it was thought that inhibiting Mgat5 expression would be useful in treating malignancies. *See* Granovsky.

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefits to the public. One such benefit is the ability to modulate expression of MGAT5 in order to modulate the sensitivity of tumor cells to cell signaling. In view of the application providing particular targets of known function for the claimed microRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requires are satisfied in accordance of Fisher and Guidelines.

(3) Credible Utility

An asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided. An assertion is credible unless (i) the logic

underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Accordingly, the invention must be operable to achieve useful results. *See Guidelines* at page 5 and *In re Swartz*, 232 F.3d 862 (Fed. Cir. 2000). The proper inquiry for determining credible utility is whether a person of ordinary skill in the art would conclude that the asserted utility is more likely than not true. Applicant respectfully submits that the record clearly shows that one of ordinary skill in the art would believe that the claimed nucleic acids may be used to modulate expression of the specific mRNA targets.

Dr. Yitzhak Pilpel, who is an expert in the field of microRNA and RNAi biology, states in the attached declaration (Appendix) that the claimed nucleic acids would likely inhibit expression of the MGAT5 mRNA transcript. Dr. Pilpel's opinion is based on a number of facts.

(a) Characteristics of microRNA-target mRNA binding

Dr. Pilpel states that researchers in the microRNA field believed that there are a number of characteristics of inhibition of protein expression via target mRNA interference by an endogenous or synthetic nucleic acid of 18-25 nucleotides in length, such as a microRNA. For example, the 5' end of the microRNA may contain a "seed" that is full complementary between the first 1-8 base pairs of the 5' of the microRNA and the target mRNA. *See* paragraphs 2 and 3, Pilpel Declaration. This seed may be conserved and is often flanked by adenosine. *See* paragraph 3, Pilpel Declaration. If there is insufficient base-pairing of the microRNA 5' seed there may be compensatory complementation at the 3' end of a microRNA and its target mRNA sequence. *See* paragraph 3, Pilpel Declaration. Finally, although not obligatory, there may be multiple binding sites for a microRNA on a mRNA target, which may enhance the binding effect of target repression. *See* paragraph 3, Pilpel Declaration.

Importantly, Dr. Pilpel states that the claimed nucleic acid sequence as set forth in SEQ ID NO: 348 and its target gene sequence of MGAT5 (as depicted in Column B, Row 3, Page 4 of Table A) are consistent with the characteristics of the microRNA:target mRNA binding described above. *See* paragraph 6, Pilpel Declaration. In view of these conserved characteristics, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 348 (Column B, Row 3, Page 4 of Table A) is likely to inhibit expression of the protein encoded by the target gene MGAT5 in view of the characteristics of microRNA:mRNA binding properties. *See* paragraph 6, Pilpel Declaration.

(b) MicroRNA algorithms

Dr. Pilpel states several effective microRNA:target algorithms have been based upon the characteristics of microRNA:target mRNA binding described above. *See* paragraph 4, Pilpel Declaration. Dr. Pilpel provides TargetScan (developed by Lewis *et al., Cell* 115:787-798 (2003)) and miRanda (developed by Enright *et al.*, *Genome Biology* 5:R1 (2003)) as examples of such algorithms. The

TargetScan algorithm predicted 15 targets of various miRNAs identified by Lewis, and 11 of the predicted interactions between a particular miRNA and target mRNA were biologically validated with a false positive rate between 22 and 31%. The miRanda algorithm was also an effective microRNA:target algorigthm, where 9 out of 10 predicted targets identified by the miRanda algorithm in Enright were biologically validated with a 24-39% false positive rate. *See* paragraph 4, Pilpel Declaration.

Importantly Dr. Pilpel states that SEQ ID NO: 348 and its target gene sequence of MGAT5 are consistent with microRNA and target mRNAs predicted by the algorithms described above. *See* paragraphs 4 and 5, Pilpel Declaration. Moreover, Dr. Pilpel states that the TargetScan algorithm detects the binding of SEQ ID NO: 348 (hsa-miR-497) to MGAT5. *See* paragraph 5, Pilpel Declaration and Row 3, Page 4 of Table A. In view of these facts, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 348 is likely to inhibit expression of the protein where co-expressed. *See* paragraph 6, Pilpel Declaration.

(c) MGAT5

Applicant further submits that MGAT5 is a credible target for trans-acting regulatory elements. Specifically, the Pilpel Declaration indicates that the nucleic acid having the sequence as set forth in SEQ ID NO: 348 has been biologically validated. *See* Row 3, Page 4, Table A. Accordingly, MGAT5 is an important target in nature by trans-acting elements such as microRNAs. Furthermore, the claimed nucleic acids are capable of binding MGAT5 with 13 out of 22 nucleotides of complementarity, as demonstrated at Table 7A, lines 15144-15148 of the specification, and as shown below.

GAM NAME	GAM ORGANISM	GAM RNA SEQUENCE	TARGET BS-SEQ	TARGET	TARGET REF-ID	TARGET ORGANISM	UTR	BINDING SITE DRAW (UPPER:TARGET;LOWER:GAM)	GAM POS
GAM353678	Human	CAGCAGCA CACTGTGG TTTGTA	CACCATGC TGCTG	MGAT5	NM_002410	Human	3	-- -- ----- CA CCA TGCTGCTG GT GGT ACGACGAC AT TT GTCAC	A

In view of the foregoing, Applicant asserts that a person of ordinary skill in the art would more than likely conclude that the claimed nucleic acids may be used to modulate expression of MGAT5, which in turn would modulate the sensitivity of tumor cells to cell signaling. Accordingly, a proper credible utility is asserted for the claimed nucleic acids. Applicant respectfully asserts that a specific and substantial utility has been demonstrated both in the specification and by what was recognized as well as established in the art at the time of filing, and the utility is credible. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 101.

c. 35 U.S.C. §112, First Paragraph

On page 10 of the Office Action, the Examiner asserts that because the claimed subject matter lacks substantial utility, the specification also does not provide an enabling disclosure. Applicant disagrees. In view of the claimed subject matter having credible, specific, and substantial utility as

described above, Applicant submits that the specification enables the claimed subject matter and respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

d. 35 U.S.C. §102

In view of NEB Random Primer 24

On pages 10-12 of the Office Action, the Examiner rejects claims 23, 25, 27-30 under 35 U.S.C. § 102(b) as allegedly being anticipated by Random Primer 24, sold by New England Biolabs in the 1998/99 catalog ("NEB"). The Examiner asserts that NEB teaches a vial containing 9 copies of every possible 24-nucleotide sequence. The Examiner alleges that the specification contains no clear or limiting definition of the term "isolated" that would clearly preclude isolated mixtures of oligonucleotides of the type sold and disclosed by NEB. Applicant respectfully disagrees and submits that the Examiner's rejection is solely an issue of whether an "isolated" nucleic acid is taught by NEB.

The term "isolated" has a clear meaning to one of skill in the art. As the Examiner notes on page 11, NEB teaches a vial containing over 2.81×10^{14} possible 24-nucleotide sequences. Even if one such tube contained a nucleic acid with the sequence of the claimed nucleic acid, NEB teaches this nucleic acid as only one among 2.81×10^{14} nucleic acids in the vial. One sequence among 2.81×10^{14} is not an isolated nucleic acid. Accordingly, NEB does not specifically teach the sequences of the instantly claimed nucleic acids.

Finally, amended claim 23 is related to a sequence of 22 nucleotides in length, and amended claim 25 is related to a sequence of 91 nucleotides. Accordingly, NEB teaches only 24-mers and does not disclose the claimed nucleic acids, and therefore does not teach all the limitations of either amended claim 23 or 25. Claims 27-30 are canceled, thereby rendering moot the rejection of these claims. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102(b) in view of NEB.

In view of US 6,582,908

On pages 12 and 13 of the Office Action, the Examiner rejects claims 23, 25, and 27-30 under 35 U.S.C. § 102(b) as allegedly being anticipated by Fodor *et al.* (U.S. Pat. No. 6,582,908; "Fodor"). The Examiner asserts that Fodor teaches a nucleic acid array comprising all possible 20-mers, thereby anticipating DNA equivalents of the instantly claimed nucleic acids. Applicant respectfully disagrees.

As discussed above, amended claims 23 and 25 are directed to isolated nucleic acids. The array of Fodor cited by the Examiner comprises nearly 1.1×10^{12} different sequences. One sequence among 1.1×10^{12} is not isolated. Accordingly, Fodor does not teach all the limitations of either amended claim 23 or

25. Claims 27-30 are canceled, thereby rendering moot the rejection of these claims. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 23 and 25 under 35 U.S.C. § 102(b) in view of Fodor.

In view of US 7,250,289

On page 13 of the Office Action, the Examiner rejects claim 23 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 7,250,289 ("Zhou"). Specifically, the Examiner asserts that Zhou discloses a 25 nucleotide DNA probe (SEQ ID NO: 669995) that is at least 70% identical to a complement of SEQ ID NO: 348. In view of amended claim 23, Applicant submits that Zhou does not teach or suggest the claimed nucleic acids. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claim 23 under 35 U.S.C. 102(e) in view of Zhou.

In view of US 7,232,806

On pages 14 and 15 of the Office Action, the Examiner rejects claims 23, 27, 28, 31, 35 and 36 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 7,232,806 ("Tuschl"). Specifically, the Examiner asserts that Tuschl discloses a 21 nucleotide DNA probe (SEQ ID NO: 19) that is at least 77.3% identical to SEQ ID NO: 348. In amended claim 23, Applicant submits that Tuschl does not teach or suggest the claimed nucleic acids. Nor does Tuschl teach or suggest the claimed vectors. As discussed above, claims 27, 28, 35 and 36 have been canceled without prejudice, thereby rendering moot the rejection of these claims. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102(e) in view of Tuschl.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: March 17, 2008

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